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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/714,852	11/18/2003	Hidenobu Senpuku	245617US0	3710

22850 7590 03/31/2008

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ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
03/31/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/714,852	SENPUKU ET AL.	
	Examiner	Art Unit	
	Stephen Kapushoc	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/11/2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim 1 is pending and examined on the merits.

Please note: The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This Office Action is in reply to Applicants' correspondence of 12/11/2007.

Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put this application in condition for allowance. Any new grounds of rejection presented in this Office Action are necessitated by Applicants' amendments. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.

This Action is **FINAL**.

Claim Objections

1. Claim 1 is objected to because of the following informalities:

Claim 1 is objected to over the multiple recitations of the phrase 'inhibition of the mutans streptococci to the surface of the tooth' where the phrase 'inhibition of adhesion of the mutans streptococci to the surface of the tooth' is likely intended as consistent with the preamble of the claim.

Claim 1 is objected to over the recitation of the phrase 'genotype correlating low mutans streptocci adhesion' (lines 12-13 of claim 1), where likely the phrase 'genotype correlating to low mutans streptocci adhesion' is intended.

Appropriate correction is required.

Withdrawn Claim Rejections - 35 USC § 112 2nd ¶ - Indefiniteness

2. The rejection of claim 1 under 35 U.S.C. 112, second paragraph, as being indefinite, as presented in the previous Office Action, is **WITHDRAWN** in light of the amendments to the claims.

Claim Rejections - 35 USC § 112

3. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is unclear over recitation of the requirement that 'the identified genotype from the subject is a genotype correlating to a high mutans streptococci adhesion to the tooth relative to the genotype correlating low mutans streptococci adhesion to the tooth'. This recitation is unclear because there is no requirement for correlating any genotype to 'mutans streptococci adhesion to the tooth'. The claim recites only, for example, that the table 'correlates genotype at the DRB1* locus and inhibition of the mutans streptococci to the surface of the tooth', where 'inhibition' is not 'adhesion'. As such it is not clear now the required correlation to adhesion is accomplished with the table as recited in the claim.

Claim Rejections - 35 USC § 112 - Enablement

4. Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it

pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not provide for a method in which the caries risk can be measured by examining adhesion of mutans streptococci to a surface of a tooth in a patient, where adhesion is correlated to DRB1*, and adhesion is measured by antibody titer of immunoglobulin A in human saliva against an antigen of SEQ ID NO: 1.

Nature of the Invention and Breadth of the Claims

Claim 1 is drawn to a method for examining adhesion of mutans streptococci (mS) to the surface of a tooth in a patient, where adhesion of mS is a measure of the caries risk. The method requires identifying the DRB1* genotype in a patient, and comparing the identified genotype with a previously determined correlation between the genotype and inhibition of mS to the surface of the tooth. The claim further requires that inhibition of mS to the surface of the tooth is determined with an anti-SEQ ID NO: 1 IgA antibody titer in saliva, where then the identified genotype indicates the patient is at risk of developing caries if the identified genotype is a genotype correlating to high mS adhesion.

Claim 1 encompasses identifying the caries risk in any animal subject, and also includes the analysis of any possible DRB1 genotype as it may be indicative of increased or decreased caries risk. The claim additionally includes any method in which the antibody titer of a secretory immunoglobulin A from saliva in humans is determined using SEQ ID NO: 1 as an antigen, and comparing this antibody value to the identified genotype. The claims further require that genotype is correlated with mS adhesion.

The nature of the invention thus requires knowledge of a robust and reliable association between several elements as follows: caries risk of an individual and mS tooth adhesion; mS tooth adhesion and anti-SEQ ID NO: 1 IgA antibody titer in human saliva; and DRB1 genotype and anti-SEQ ID NO: 1 IgA antibody titer in human saliva. Knowledge of all of these asserted association is required in the claimed method wherein the recited table requires genotypes related to adhesion, where adhesion is related to IgA titer, and thus genotype is indicative of adhesion as determined by IgA titer and indicative of caries risk.

State of the Prior Art, Level of Skill, and Level of Unpredictability

The prior art concerning to the investigation of DRB1* genotypes and phenotype teaches the examination of particular genotypes with regard to several diseases that involve immune system components. Though the level of skill with regard to identification of different DRB1* genotypes in humans is high, results from attempts to demonstrate an association between any particular genotype and a disease state are indicative of an even higher level of unpredictability. Some of the unpredictability in correlating DRB1* genotype to disease predisposition is due to the highly polymorphic nature of the gene. Epplen et al (1997a) teaches the extremely polymorphic nature of DRB1*, and indicates that DRB1* is the most polymorphic protein-coding locus in man and all vertebrates (p.399 – Abstract).

Acton et al (1999) exemplifies the unpredictable nature of this art. Acton et al reports (p.984 – Abstract; p.988, left col., last ¶) no significant associations were observed between and DRB1 allele and the DMFS index (a measure of caries risk), and

further indicates that an association between dental caries and DRB1 alleles was not observed by investigators who assessed military recruits from the Netherlands (p.988, left col., last ¶). Additionally, the prior art of Ozawa et al (2001) indicates that in an analysis of HLA-DRB1 alleles, no allele frequencies showed significant differences between a caries-free group and a caries-susceptible group (Page 2 – Abstract). Similarly, the post filing art of Chiba et al (2005) demonstrates the difficulty in correlating DRB1 alleles with caries risk. Chiba et al teaches that it is not predictable which DRB1 alleles will be associated with levels of cariogenic bacteria, or cariogenic bacteria levels as stratified by caries-resistant versus caries-susceptible subgroups. Of particular relevance to the instant claims, the post-filing art of Tsuha et al (2004) indicates that, in an analysis of PAc (361-386) IgA titer (relevant to instant SEQ ID NO: 1), number of decayed, missing, or filled teeth (DMFT index), and concenctration of cariogenic mS, there is no significant associtiation between these three elements (Table 2; p.396 - Correlations between DRB1 genotypes and anti PAc (361-386 peptide antibodies). Thus both the prior art and post filing art teaches the unpredictablility in attempting associations between DRB1 genotype, caries risk, mS adhesion, and any antibody titer.

Epplen et al (1997b) teaches the analysis of HLA-DRB1 genotypes in attempts to determine predisposition to multiple sclerosis (MS), early onset pauciarticular arthritis (EOPA) and rheumatoid arthritis (RA). The reference teaches the complex nature of using HLA-DRB1 genotypes as indicators of disease predisposition, and shows that it is often necessary to examine other genetic factors in addition to HLA-DRB1 genotype (Fig4; p.1583 – HLA and disease association: functional aspects vs. linkage

disequilibrium). In the examination of MS predisposition, the reference teaches the analysis of more than 600 MS patients and the respective number of controls (p.1582, right column, l.21). The reference further teaches that while DRB*15 correlates with an increased risk of MS, the increased risk of DRB1*03 individuals is hardly recognizable (p.1582, right column, l.31). However, when the DRB1*03 allele is found together with a certain allele of another gene (TCRBV6S3), the risk of developing MS increases 22-fold (p.1583, left column, l.1).

Wyand et al (2000) teaches the use of HLA-DRB1 alleles as predictive indicators of RA. The reference indicates that different alleles (alone and in combination) have been associated with different forms of the disease (p.214, left column, l.7); but the reference also indicates that showing an association between an allele and a phenotype is not necessarily a sign of the extent to which a polymorphism can be used as a biomarker to predict disease course (p.214, left column, l.20). The reference further teaches that proper analysis of the association between HLA allele and disease requires sufficient patient numbers to control for disease and treatment variables, and to assess the impact of polymorphisms and gene dosing (p.214, left column, l.21).

Walkyria et al (2001) teaches the analysis of HLA alleles with regard to type 1 diabetes in a Brazilian population. The study concludes that there are several haplotypes which include specific DRB1 alleles that occur with increased frequencies in patient groups, as well as a particular DRB1 genotype which correlated to the highest risk for type I diabetes (p.1226 – Abstract). To reach these conclusions, the study utilized a case-control analysis of 181 individuals, which included 70 patients and 111

healthy subjects, in which multiple genes were simultaneously analyzed (p.1227 – Subjects, HLA typing). The conclusion that DRB1*03 and DRB1*04 alleles are indicators of type 1 diabetes susceptibility are drawn from the statistical analysis of the occurrence of these alleles in multiple patients versus controls (p.1229 – predisposing and protective alleles; p.1230 – Table 2). However, pointing to the unpredictability of the utility of DRB1*401 as a susceptibility marker, the reference teaches that the effect of DRB1*401 is variable depending on the population studied (p.1231, left column, l.14). The reference also points out the unpredictability of the effect of different alleles in different populations when teaching the lack of a protective effect of a haplotype that includes DRB1*1501 in the Brazilian population, indicating that such a haplotype usually confers a dominant protective effect in most populations; and that although the population under study was small, the DRB1*1501-containing haplotype was found in two diabetic patients (p.1232, left column, l.5).

Collectively, these studies teach the requirements that enable the determination of an association between a DRB1 allele and a phenotype. Such a determination requires a case-control study with a population large enough to allow a statistically significant analysis of the data. The studies also show the importance of examining other genes (e.g. establishing haplotypes) when investigating DRB1-phenotype associations. Importantly, the studies show that given the enormous number of DRB1 alleles, not every allele will be predictive. Determining an association requires finding a particular allele multiple times in affected or control subjects, and it is a preponderance

of alleles in a particular group, not just a single instance of an allele in a single subject, which serves as the basis of the determination.

Amount of Direction Provided and Working Examples

The instant application provides no working example of the use of the claimed method for examination of the caries risk. Furthermore, the specification does not provide any analysis or evidence suggesting a reliable predictive relationship between HLA DRB1 alleles, IgA titer, mS tooth adhesion, and caries risk. As noted previously in the rejection, knowledge of such a relationship is essential for the practice of the claimed invention.

The specification of the instant application provides an example (p.13 – Example 1) in which DRB1* genotypes and anti-PAC antibodies were analyzed. The specification teaches the determination of HLA-DRB1 genotype via a PCR-RFLP method. The specification teaches the use of several primers (p14-15) for DRB1 amplification:

Primers	Alleles amplified
DR3 and AmpB	DRB1*03, 08, 11, 12, 13, 14
DR4-like and AmpB	DRB1*1122, 1410, 1130

The specification does not specifically describe the use of any other primers for the amplification of any other HLA-DRB1 alleles. The specification further describes the treatment of the amplified DRB1 fragments with restriction enzymes, but does not indicate what type of restriction pattern is indicative of any particular genotype.

The specification also teaches the measurement of secretory anti-PAc antibodies in human saliva. The specification teaches an ELISA assay (p.17) in which a PAc peptide, corresponding to amino acids 361-386 of the S. mutans PAc protein, is used as an antigen, and alkaline phosphatase-labeled anti-human IgA is used to detect to detect anti-PAc antibodies. The specification teaches that a high level of anti-PAc antibodies is indicative of a low caries risk (p.11 l.4).

The specification teaches the comparison of HLA-DRB1 genotypes and anti-PAc antibody levels in the saliva of five individuals (p.20 and Table 1). However, the specification teaches that the five individuals (each of which were placed into one of two groups: High antibody value and Low antibody value) all have unique DRB1 alleles. There is no statistical analysis of the data, and in fact the results indicate that no particular genotype is found in more than one individual within either the High versus Low antibody groups, or within the entire population studied; there is no repeated finding of any particular genotype that would lead one to believe that such a genotype would indicated a predisposition or susceptibility for developing caries. In fact, the example provided in the instant specification does not indicate there exists any correlation between any HLA-DRB1 genotype and antibody levels or caries risk. Furthermore, there is no validation of the predictive use of DRB1 genotypes in examining caries risk, nor any analysis of whether or not the individuals in the study actually developed caries.

The instant application asserts (p.5 and p.10) that an anti-PAc antibody inhibits the adhesion of mS to the tooth surface, and that the presence of the antibody can be

related to the presence of a DRB1 genotype in an individual. However, the instant specification provides no analysis of the correlation of any genotype with mS adhesion. Further there is no reliable evidence presented to show a reliable association between genotype, IgA titer, and mS adhesion.

Quantity of Experimentation Needed to Use the Invention

The quantity of experimentation required to use the claimed invention is high. If one wished to use the methods outlined in the instant specification to determine caries risk, one would first have to conduct a larger scale case-control study to discover which DRB1 alleles are present in caries-sensitive subjects versus subjects resistant to caries. Such a study may be focused on a general population or a specific subpopulation (e.g.: ethnic or geographic), and may also include corrections for environmental factors such as diet or hygiene. Such a study would have to be large enough in scope to detect correlations between any of the many different DRB1 alleles and a risk of caries; as the specification indicates, solving all combinations of DRB1 dimers would allow for accurate evaluation of the caries risk (though the instant specification provides information about DRB1 alleles from only five individuals). One would also have to analyze any possible genotype as it relates to antibody titer of immunoglobulin A against the antigen consisting of SEQ ID NO: 1 and further establish that antibody titer is indicative of both mS tooth adhesion and caries risk. Validation of any specific alleles alleged to be useful for prediction of an increased caries risk would have to go beyond just showing a correlation with increased antibodies or higher levels of S. mutans in the

oral cavity, and have to show an actual correlation with mS adhesion and increased caries development.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and scope of the claims, the state of the art and its high level of unpredictability, the lack of guidance by the applicant and the lack of a working example, it is the conclusion the an undue amount of experimentation would be required to use the invention as claimed.

Response to Remarks

5. Applicants have traversed the rejection of claims under 35 USC 112 1st ¶ for lack of enablement. Applicants argue (p.4 of the Remarks) that the one element of caries risk is the assessment of initial adhesion of mS to the tooth surface, where the claimed method assesses antibody titer as a measure of adhesion. This argument is not found to be persuasive because, as noted in the rejection, the specification provides not evidence as to the required relationship between DRB1* genotpye and mS adhesion as measured by IgA titer. In fact, the cited Tsuha et al (2004) provides evidence that there is no reliable association between genotype, mS adhesion, and caries risk, all of which is required by the claimed method. That the claimed method is not a test of whether an individual is actually suffering from caries, but an assessment of the relative risk of caries development is not sufficient to overcome the lack of evidence of an association in the specification, and the evidence of unpredictability as taught in the post-filing art.

Applicants argue (p.4-5 of Remarks) that the claimed method requires preparing a table that correlates DRB1* genotype to antibody titer, and that antibody titer is a measure of mS on the tooth surface, where the level of mS on the tooth surface in an indicator of risk for caries. Applicants assert that the required technologies (i.e. genotyping and determining antibody titer) are common and well-used in the field, And thus undue experimentation is not required to make and use the invention as claimed. The arguments and assertions are not found to be persuasive. The claimed invention indeed requires a table that correlates genotype with mS adhesion, and requires that IgA titer is indicative of adhesion and that adhesion is indicative of caries risk, such that genotype is indicative of caries risk. However, neither the instant specification nor the prior or post-filing art support the notion that in fact all of these required associations can be found. Most convincingly, Tsuha et al indicate that there is no association between DRB1* genotype or IgA titer and caries risk (as is ultimately required by the claimed method) or mS adhesion (as measured by mS concentration). The examiner maintains, for the reasons presented in the instant rejection and the reasons of record as set forth in the Response to Remarks of the previous Office Action) that there would be required and undue amount of experimentation on the part of the skilled artisan to make and use the claimed invention.

With regard to the rejection of claims for lack of enablement, and the unpredictability of the associations required, it is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable (See Brenner v. Manson, 383 U.S. 519, 536,

148 USPQ 689, 696 (1966) that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."). Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.

In instant case the examination of mS adhesion as a measure of carries risk by identifying DRB1* genotype is not considered routine in the art. The experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore considering the state of the art and limited amount of guidance provided in the instant specification, one of skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

The rejection as set forth is **MAINTAINED**.

Conclusion

6. The claim is not allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH

shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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